REMARKS

Claims 18-24 and 26-28 are pending.

Support for the language in claim 21 is found on page 7, lines 25-34, page 9, lines 18-20, page 34, lines 19-20, and page 35, lines 1-2 of the specification. Claim 26 has been rewritten in independent format, incorporating the amended language of claim 21 from which it depended.

No new matter is added by this amendment.

Double Patenting

Applicants request that the obviousness-type double patenting rejection against claims 18-29 be deferred until the claims are indicated to be otherwise in condition for allowance.

Information Disclosure Statements

In the Information Disclosure Statement stamped May 3, 1999, sheet 2 of 6 has not been initialed and dated by the examiner. We are providing a further copy of this sheet, and request that the examiner indicate consideration of these documents by returning a signed, dated copy of this sheet.

In addition, Applicants are submitting herewith a Supplemental Information Disclosure Statement to supply copies of a related, co-pending application and a paper, Lebkowski, et al, Molecular and Cellular Biology, 8(10):3988-3996 (October 1988). Consideration of these documents is requested.

Prior Art Rejections

Claims 18-21 have been rejected under 35 USC §102(a) as being anticipated by Gouras, et al, Neurobiology of Aging (1996).

Applicants respectfully traverse this rejection.

Gouras contains no teaching or suggestion of a rAAV which contains no greater contamination with adenoviral helper virus than is obtained by subjecting the rAAV to four rounds of cesium chloride gradient centrifugation. The rAAV of the

the rAAV to four rounds of cesium chloride gradient centrifugation. The rAAV of the invention delivers transgene at a detectable level in the absence of a cytotoxic immune response directed against the cells in the patient transduced with the rAAV.

Reconsideration and withdrawal of this rejection is requested.

> Claims 18-25 have been rejected under 35 USC §103(a) as being unpatentable over Podsakoff et al, US Patent 5,858,351, taken in view of Chiorini, et al, US Patent 5,693,531. Podsakoff refers to the construction of an AAV vector containing erythropoietin. Chiorini teaches that prior to be delivered to a subject, rAAV particles must first be transduced *in vitro* into cells and it is the transduced cells which may be delivered to the subject.

Applicants respectfully traverse this rejection. The teachings of Chiorini direct one of skill in the art away from its combination with Podsakoff. However, even if these documents are combined, there is no teaching or suggestion of a composition comprising rAAV suspended in a carrier, in which the level of contaminating adenoviral helper virus is no greater than is obtained by subjecting the rAAV to four rounds of cesium chloride gradient centrifugation.

Podsakoff contains no teaching or suggestion of the use of ApoE for the treatment of atherosclerosis. Podsakoff teaches purifying rAAV by a single cesium chloride isopyknic gradient centrifugation and isolating the fraction with average density of approximately 1.38 g/ml. However, following this step, Podsakoff teaches heating to inactivate contaminating helper virus [col. 18, lines 26-35]. This heating step may render the helper virus incapable of replication and infection. However, heating and inactivation does not affect the antigenicity of the adenoviral helper virus. Thus, Podsakoff, whose preparation may contain inactivated adenoviral helper virus, does not even recognize the problem which is solved by the present invention.

Chiorini does not teach or suggest the use of rAAV particles for direct administration to a subject and thus, teaches away from its combination with Podsakoff. (In contrast, the present invention provides for direct delivery of rAAV

particles suspended in a suitable carrier.) Chiorini does not teach or suggest rAAV in which the level of contaminating helper virus is no greater than that obtained by subjecting the rAAV preparation to four rounds of cesium chloride gradient centrifugation.

> Claims 26 - 29 have been rejected under 35 USC §103(a) as being unpatentable over Kaplitt et al, US Patent 6,162,796, taken with either Kashyap et al, J. Clin. Invest., 96:1612-1620 (Sept. 1994) (Ref. CV of Paper No. 11) or Kashyap et al, (Circulation, 1994). Kaplitt refers to the use of adeno-associated virus vectors for the transfer of gene to the heart and vasculature. The Kashyap documents refer to intravenous infusion of a recombinant adenovirus containing human apolipoprotein E (apoE) in apoE-deficient mice.

Applicants respectfully traverse this rejection. In summary, the Kashyap documents teach away from the combination of their teachings with Kaplitt. However, even if the teachings of the Kashyap documents are combined with Kaplitt, this combination fails to provide the necessary suggestions to render the present invention obvious.

As noted by the examiner, Kaplitt does not teach or suggest the gene encoding human ApoE. The examiner refers to a passage on column 3, lines 15-30, as support for reliance on Kaplitt. However, the referenced passage in Kaplitt refers to a method of producing rAAV without detectable wild-type helper AAV. Kaplitt does not teach or suggest rAAV which is free of detectable levels of helper *adenoviral* vectors, nor does Kaplitt teach or suggest a method which would achieve such a result. This suggestion is not provided by the combination of the Kashyap documents with Kaplitt.

The Kashyap documents do not teach or suggest rAAV vectors. Nor does either Kashyap document teach or suggest intramuscular delivery of apoE. Given the success reported by Kashyap, there would be no motivation for one of skill in the art to deliver apoE via a route other than intravenous delivery, or via another vector. However, even if such motivation could be found, it is significant that the Kashyap documents do not report on or recognize the problems associated the immune response generated to adenoviral vectors.

The combined teachings of Kaplitt and Kashyap do not suggest rAAV in which the level of contaminating helper virus is no greater than that obtained by subjecting the rAAV preparation to four rounds of cesium chloride gradient centrifugation. Nor do the teachings of these documents suggest a method of using such an rAAV preparation for the purpose of delivering ApoE to a patient for treatment of atherosclerosis. It is only the inventors who recognized the problem associated with the use of rAAV preparations contaminated with adenoviral helper virus, and it is only the present invention which provides a solution to this problem.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix A is captioned "**Version With Markings to Show Changes Made**".

Attached hereto is a clean copy of all of the pending claims. The attached Appendix B is captioned "**Clean Copy of Pending Claims Without Markings**".

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,

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Appendix A

Version with Markings to Show Changes Made

In the claims:

Claim 21 has been amended as follows:

21. (Twice Amended) A composition comprising a recombinant adeno-associated virus (AAV) [~~is~~] suspended in a biologically compatible carrier,

wherein said recombinant AAV comprises (a) 5' AAV inverted terminal repeats (ITRs), (b) nucleic acid sequences encoding human [~~apoliprotein~~] apolipoprotein E (ApoE), and (c) 3' AAV ITRs, and

wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation, and wherein the ApoE is expressed in the absence of a cytotoxic immune response directed against recombinant AAV-transduced cells expressing the ApoE.

Claim 25 has been cancelled.

Claim 26 has been amended as follows:

26. (Amended) A method of delivering apolipoprotein E (apoE) to a patient in need of treatment of atherosclerosis, said method comprising the step of

administering to the patient a composition [~~according to claim 21 to the patient~~] comprising a recombinant adeno-associated virus (AAV) suspended in a biologically compatible carrier,

wherein said recombinant AAV comprises (a) 5' AAV inverted terminal repeats (ITRs), (b) nucleic acid sequences encoding human apoliprotein E (ApoE), and (c) 3' AAV ITRs, wherein the level of contaminating adenoviral helper virus is no greater than that obtained by subjecting said recombinant AAV to four rounds of cesium chloride gradient centrifugation, and wherein the ApoE in said composition is expressed in the patient in the absence of a cytotoxic immune response directed against recombinant AAV-transduced cells expressing the ApoE.

Claim 29 has been cancelled.